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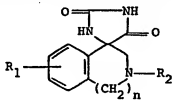
(54) **Benzoazacycloalkyl-spiro-imidazolidines**

(57) The present invention provides a compound of the general formula:



I

in which

— R_1 represents a halogen or a hydrogen atom, or a hydroxy or methoxy group,

— R_2 represents a hydrogen atom, a lower alkyl radical, a phenyl-lower alkyl radical, a lower alkanoyl radical or a *p*-toluenesulphonyl group, and

— n represents 1 or 2,

in the racemic form or as an optical isomer, or salts thereof and a process for their preparation. These compounds are useful in the treatment of diabetes.

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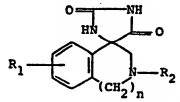
SPECIFICATION

Benzoazacycloalkyl-spiro-imidazolidines, their preparation and the pharmaceutical compositions containing them

The present invention relates to benzoazacycloalkyl-spiro-imidazolidines, a process for preparing them, and pharmaceutical compositions containing them.

The invention provides benzoazacycloalkyl-spiro-imidazolidines of the general formula:



I

in which:

R_1 represents a hydrogen or a halogen atom or a hydroxy or a methoxy group,

R_2 represents a hydrogen atom, a lower alkyl radical, a phenyl-lower alkyl radical, a lower alkanoyl radical or a *p*-toluenesulphonyl group, and

n represents 1 or 2;

and salts thereof.

Salts of compounds of the general formula I may be obtained with mineral or organic bases, or may be acid addition salts (except when R_2 represents an alkanoyl radical or *p*-toluenesulphonyl group) obtained with, for example, mineral acids. Preferably, the salts are physiologically tolerable.

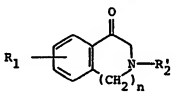
Because the compounds I have an asymmetric carbon atom (spiro bond), they may exist in racemic form, or as optical isomers, and these individual isomers, as well as the racemates, form part of the invention. Thus, it should be understood that the structural formulae and written nomenclature of the compounds described and claimed herein include, unless otherwise indicated, the individual isomers and the mixtures of the isomers.

The term "lower" used in connection with alkyl radicals or moieties or with alkanoyl radicals denotes such radicals and moieties that have from 1 to 4 carbon atoms. Thus, for example, R_2 may represent a formyl, acetyl or propionyl group or a benzyl group.

Preferred compounds are those in which R_2 represents a hydrogen atom.

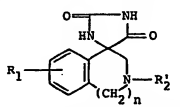
The radical represented by R_1 may be in any free position on the benzene ring, for example the 6, 7 or 8 position. Compounds with a 7-methoxy or a 6- or 8-halo substituent should especially be mentioned.

The present invention also provides a process for preparing a compound of the general formula I or a salt thereof, which comprises condensing a ketone of the general formula:



II

in which R_2' has the meaning given for R_2 above except that it may not represent a hydrogen atom, and R_1 and n have the meanings given for formula I, with an alkali metal cyanide in the presence of ammonia or of an ammonium salt, to provide a spiro-hydantoin of the general formula:



I'

in which n, R_1 and R_2' have the meanings given for formula II, and, if desired, converting a compound of the general formula I' into a compound of the general formula I in which R_2 represents a hydrogen atom and/or into another compound of the general formula I or into a salt thereof. For example, a compound of the formula I' may be debenzylated to give a compound with the formula I in which R_2 represents H, and this latter may be submitted to an acylation by means of a lower alkanoic acid halide or *p*-toluene sulphonyl halide, to obtain the corresponding compound with the formula I in which R_2 represents a lower alkanoyl radical or *p*-toluenesulphonyl group.

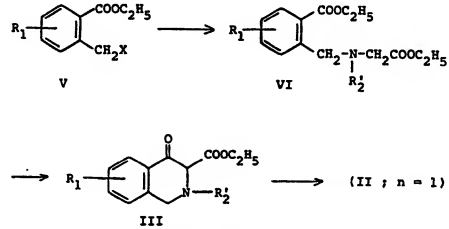
The condensation reaction of the ketone (II) with the alkali metal cyanide may be carried out for

example under the usual conditions of the Strecker reaction, in the presence of ammonia or of an ammonium salt in a polar solvent, such, for example, as alcohol, at boiling point and if necessary under pressure.

Debenzylation of the spiro-hydantoin (I') may be carried out for example by hydrogen in the presence of a catalyst such, for example, as Pd/C in a polar solvent.

Acylation may be carried out for example in the presence of an acid acceptor, which can serve as a solvent, for example pyridine.

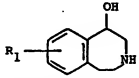
Starting materials of the general formula II in which n represents 1 (isoquinolones) are described in the literature (The Chemistry of Heterocyclic Compounds, vol. 38.1, p. 215—216, Interscience, Wiley Editor), or they may be prepared starting from benzoic esters according to the following reaction scheme:



In these various formulae, R_1 and R'_2 have the same meanings as in formula II and X represents a halogen atom, preferably Br.

The benzoic ester (V) may for example be condensed with an N-substituted ethyl glycinate in the presence of an acid acceptor such, for example, as triethylamine at reflux, then the diester (IV) cyclised to the ketone (III) by means of an alkaline alcoholate such, for example, as sodium ethylate in ethanol at reflux. The ketone (III) may then be decarboxylated by a strong acid in an aqueous medium to give the ketone derivative (II; n = 1).

Starting materials of the general formula II in which n represents 2 (benzazepinones) may be prepared starting from the corresponding alcohols of the general formula:



VI

in which R_1 has the same meaning as in formula I; the synthesis of such alcohols is described by M. LENNON et al., (J. Chem. Soc. 1975, 622). These compounds are acylated, alkylated or aralkylated on the nitrogen atom, and then the hydroxy group is oxidised to provide the corresponding ketone (II; n = 2).

The following Examples illustrate the preparation of the compounds according to the invention.

EXAMPLE 1

6-chloro-2-benzyl-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione

a) Ethyl N-(4-chloro-2-ethoxycarbonyl-benzyl)-N-benzyl-glycinate.

55.5 g (0.2 M) of ethyl 5-chloro-2-bromoethyl-benzoate is dissolved in 270 ml of ethyl oxide taken to reflux and 34.78 g (0.18 M) of ethyl N-benzylglycinate as well as 18.62 g (0.184 M) of triethylamine are added by successive fractions over 12 hours, and left at reflux for a total of 35 hours. After cooling, 150 ml of water and 80 ml of 2.5 N NaOH are added. The organic phase is decanted and submitted to an acid/base treatment. 43.8 g of product is obtained in the form of an oil (Yield 61%).

I.R.: C = O 1730 cm^{-1}

NMR: 8H (ar.) 7.5 ppm 4H (q) 4.3 ppm
2H (s) 4.2 ppm 2H (s) 3.8 ppm
2H (s) 3.3 ppm 6H (t) 1.3 ppm

b) 6-chloro-3-ethoxycarbonyl-2-benzyl-1,2,3,4-tetrahydro-4-isoquinolone.

26.9 g (0.069 M) of the crude ester obtained at a) above is dissolved in 350 ml of benzene and over 90 minutes this solution is poured into a solution of 2.1 g of sodium ethylate in 50 ml of ethanol. The reaction mixture is taken to reflux for one hour, then cooled and treated with dilute hydrochloric acid until neutral. The benzene phase is decanted, washed with water, dried and the solvent evaporated. 22.9 g of crystallised product is obtained.

M.P. = 71—76°C (MinIKofler).

After recrystallisation from 40 ml of ethanol, 19 g of product is obtained (Yield 80%), M.P. = 75—77°C (M.K.)

I.R.: C = O (ester) 1640 cm^{-1} C = C—OH 1610 cm^{-1}

NMR: Confirmation of the enol form; 1H exchangeable at 11.6 ppm.

c) 6-chloro-2-benzyl-1,2,3,4-tetrahydro-4-isoquinolone.

26.1 g (0.076 M) of the compound obtained at b) is added to 130 ml of ethanol and 400 ml of 10 N (aqueous) HCl and taken to reflux for 12 hours. After elimination of the greater part of the ethanol, the hydrochloride of the compound sought precipitates. After separating, washing and drying, 19 g of crude product is obtained.

The base is obtained by partition between dichloromethane and 5 N sodium hydroxide.

16.1 g M.P. = 82—83°C (M.K.)

Recrystallising from 35 ml of isopropyl oxide provides,
14.2 g (Yield 69%) M.P. = 83—85°C (M.K.)

I.R.: C = O 1690 cm^{-1}

NMR: 8H (ar.) 7—8 ppm 4H (s) 3.8 ppm
2H (s) 3.4 ppm

d) 6-chloro-2-benzyl-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione.

13.8 g (0.051 M) of isoquinoline obtained at c), 4.97 g (0.0765 M) of potassium cyanide and 24.48 g (0.255 M) of ammonium carbonate in 170 ml of ethanol are put into an autoclave and taken to 115° for 22 hours. After cooling, and evaporation of the solvent, the residue is taken up by 50 ml of water. The solution is acidified to pH 1, and by separating, washing with water and then with methanol, 13.2 g of product is obtained.

(Yield 76%) M.P. = 260°C (M.K.)

I.R.: C = O 1720 cm^{-1} to 1770 cm^{-1}

NMR: 8H (ar.) 7—7.5 ppm 4H (m) 3.5—3.8 ppm
2H (s) 2.9 ppm

EXAMPLE 2

6-chloro-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione

3.1 g (0.009 M) of the spiro-hydantoin obtained at Example 1 is hydrogenolyzed in 60 ml of acetic acid, at 60°C under ordinary pressure, and in the presence of 500 mg of Pd at 10% on charcoal.

After absorption of the theoretical volume of hydrogen, the solvent is filtered and evaporated. The residue is crystallised from a water-ethanol mixture. 1.4 g of product is obtained.

(Yield 63%) M.P. = 234—238°C (M.K.)

EXAMPLE 3

6-chloro-2-acetyl-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione

2.51 g (0.01 M) of the compound obtained at Example 2 is acetylated by acetyl chloride in the presence of pyridine at ambient temperature. The crude acetylated product is isolated and crystallised from methanol. 1.4 g is obtained.

M.P. = 252—254°C (M.K.)

I.R. (DMSO): NH 3500—2500 cm^{-1}

C = O 1700 and 1765 cm^{-1} (imidazolinone)

C = O 1640 cm^{-1} (acetyl).

EXAMPLE 4

3-acetyl-2,3,4,5-tetrahydro-benzo[d]1-H-azepine-5-spiro-4'-imidazolidine-2',5'-dione

a) 1-hydroxy-3-acetyl-2,3,4,5-tetrahydro-benzo[d]1-H-azepine.

7 g (0.043 M) of 1-hydroxy-benzo[d]perhydro-azepine, prepared according to LENNON and al (J. Chem. Soc. 1975, 622) is acetylated by acetyl chloride at ambient temperature. The acetylated derivative is isolated and crystallised from acetonitrile.

5.5 g is obtained (Yield 63%) M.P. = 113—116°C (M.K.)

I.R OH 3200 cm^{-1} CO 1620 cm^{-1}

b) 3-acetyl-2,3,4,5-tetrahydro-benzo[d]1-H-azepin-1-one

4.5 g (0.002 M) of acetyl-benzazepinol obtained at a) is oxidised by 15.4 g of complex $CrO_3 \cdot 2$ pyridine in 200 ml of acetone. After the usual treatment, 3 g of product is isolated after distillation under vacuum.

B.P.: 0.001 mm (pressure) = 180°C

I.R.: CO (amide 1650 cm^{-1} CO (ketone 1690 cm^{-1}

c) 3-acetyl-2,3,4,5-tetrahydro-benzo[d]1-H-azepine-5-spiro-4'-imidazolidine-2',5'-dione

By operating as in Example 1 d) but starting with 3.5 g (0.017 M) of perhydroazepinone obtained at b) above, (instead of isoquinoline) 1.67 g (0.026 M) of KCN and 8.16 g (0.085 M) of $(NH_4)_2CO_3$, 2.4 g of the product sought is obtained after crystallising from methanol.

M.P. = 268—276°C (M.K.)

I.R.: CO (hydantoin) 1770 cm^{-1} and 1720 cm^{-1}
CO (acetyl) 1660 cm^{-1}

EXAMPLE 5

Optical isomers of 6-chloro-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione

a) Camphosulphonate of the (*d*) isomer

100 g (0.336 M) of the racemic compound obtained according to Example 2, 78 g (0.336 M) of (*l*)-10-camphosulphonic acid, 1300 cm^3 of water and 400 cm^3 of ethanol are taken to reflux until complete dissolution. The solution obtained is concentrated to dryness which yields 162 g of the product sought, the product is crystallised from 3200 cm^3 methanol, and 70.7 g precipitates after one night in the refrigerator at 3°C. A second crystallisation from 2950 cm^3 methanol, 24 hours in the freezer at —18°C yields 54.6 g of (*d*)-6-chloro-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione, (*l*)-10-camphosulphonate.

M.P. = 257°C (decomposition)

$\alpha_{589}^{21°} = +24.6 \quad \alpha_{436}^{21°} = +44$ (0.5% in CH_3OH)

b) (*d*)-isomer

13.8 g (0.0285 M) of the camphosulphonate obtained hereabove is suspended in 145 cm^3 of an aqueous solution of 2% triethylamine. The suspension is heated on a water bath until a neutral pH solution is obtained, which is left overnight in the refrigerator at 3°C; 6.8 g of (*d*)-6-chloro-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione precipitates.

M.P. = 252°C (decomposition and sublimation)

$\alpha_{589}^{22°} = +44.4 \quad \alpha_{436}^{22°} = +86.4$ (0.4% in CH_3OH)

c) Hydrochloride of the (*d*)-isomer

6.4 g (0.0255 M) of the free base obtained above is suspended in 15.4 cm^3 of 1.65 N hydrochloric acid. After 20 minutes contact, then 3 hours in the refrigerator (3°C), 6.7 g of the hydrochloride is obtained.

M.P. = 245°C

$\alpha_{589}^{22°} = +78.3 \quad \alpha_{436}^{22°} = +177.7$ (0.5% in CH_3OH)

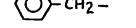
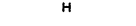
d) (*l*)-isomer

The operation is exactly the same as for the separation of the (*d*)-isomer above, but starting from (*d*)-10-carphosulphonic acid (instead of the (*l*)) so as to obtain the (*l*)-6-chloro-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione, (*d*)-10-camphosulphonate. The physical data are of course the same as those of the (*d*)-isomer, the rotatory power being inverted.

The optical pureness of the isomers was verified and was found higher than 98%.

The compounds obtained in the preceding Examples as well as other compounds with the formula I given by way of non limitative examples and prepared in a similar manner are summarised in the following table. The formula of each of the compounds has been verified by centesimal analysis and their structure by I.R. and NMR.

TABLE

Compound No.	n	R_1	R_2	m.p. (°C)	Preparation
1	1	7–CH_3O		243–6	as ex. 1
2	1	7–CH_3O	H	245–9	as ex. 2
3	1	7–CH_3O		208–10	as ex. 1
4	2	H		262–3	as ex. 1
5	1	7–CH_3O	CH_3CO	235–5 (HCl)	as ex. 3
6	1	6–Cl	H	234–8	example 2
7	1	6–Cl		260 (dec.)	example 1
8	1	6–Cl	CH_3CO–	252–4	example 3
9	2	H	CH_3CO–	268–76	example 4
10	1	6–Cl	CH_3CH_2CO–	225–7	as ex. 3
11	1	H	H	260 HCl (dec.)	as ex. 2
12	1	H		255–60	as ex. 1
13	1	6–F		275–80 (dec.)	as ex. 1
14	1	6–F	H	265 (dec.)	as ex. 2
15	(d) Isomer of compound No. 6			252 (dec.)	example 5b
16	(l) Isomer of compound No. 6			252 (dec.)	example 5d
17	1	8–Cl		195–207 (HCl)	as ex. 1
18	1	8–Cl	H	270 (dec.) (HCl)	as ex. 2

Pharmacological study of the compounds according to the invention

1. The compounds according to the invention have been tested for their inhibiting action on aldose-reductase extracted from the crystalline lens of rats according to the technique described by S. HAYMAN and J. H. KINOSHITA, J. Biol. Chem. *240* (1965) 877, modified by S. D. WARNA and J. H. KINOSHITA, Biochemical Pharmacology *5* (1976), 2505—2613.

The products according to the invention dissolved in a pH 6.2 buffer are incubated at 25°C in a stoppered recipient containing the aldose-reductase extracted from the crystalline lens of CD River rats. After 10 minutes of contact the substrate is added and the activity of the enzyme is judged by the disappearance from the medium of the co-factor nicotinamide adenine dinucleotide phosphoric acid (NADPH) reduced according to the reaction:

$$D-\text{glucose} + NADPH \rightarrow \text{Sorbitol} + NADP + H^+$$

The enzyme activity is calculated by determining the quantity of NADPH which has disappeared. The results are expressed as a percentage of the enzyme activity of the preparation in the absence of any inhibitor. Under these conditions the minimum dose which inhibits the aldose-reductase by 100% and the minimum which inhibits the enzyme activity by 50% can be determined.

The compounds according to the invention were tested at concentrations varying between 10^{-8} and 10^{-5} M. Generally, inhibition of the enzyme preparation by 50% was obtained with a concentration of 10^{-7} M.

2. The toxicity of the compounds according to the invention is very weak and the LD_{50} determined on Swiss mice is greater than 1 g/kg by the intraperitoneal route.

3. The activity *in vivo* of the compounds has been studied on rats rendered diabetic by intravenous injection of streptozotocine at 65 mg/kg.

The products tested were administered in suspension in a gummy solution (20%) by the oral route morning and evening. The animals were induced to eat their food between hours 8 and 16.

After 7 days treatment, the animals were killed by decapitation. The blood was gathered for measurement of the glycaemia by the glucose-oxidase method. The crystalline lenses were removed immediately after death, rapidly weighed and plunged into liquid nitrogen. The frozen crystalline lenses were pulverized in an aqueous solution of sedoheptulose utilised as an internal standard for gaseous phase chromatography determination. The proteins were precipitated. After centrifuging, the supernatant was recovered and lyophilized. The dried extract was silylated by TMCS/HDMS and taken up in heptane for chromatography by means of a "Hewlett Packard 5710" chromatograph under the following conditions: Detection FID, column 2.5 m, 3 mm, 9% E.G.S. chrome G AWDMCS 80—100 mesh (0.15—0.18 mm) temperature 170°C, gas vector: nitrogen (30 ml/mn).

The results showed that the compounds of the invention, at a daily dose of 2 × (1 to 5) mg/kg p.o., reduced by 70 to 100% the content of sorbitol in the crystalline lens of rats rendered diabetic (glycaemia 4.0 ± 0.4 g/l).

Therefore the compounds according to the invention possess useful pharmacological properties. In particular, the exhibit inhibiting properties for the aldose-reductase enzyme, the principal enzyme which controls the regulation of the metabolism of the aldoses and, in particular, the aldhexoses such as glucose and galactose, by transforming them into the corresponding polyol (sorbitol or galactitol for example) in the human organism.

Excess functioning of such an enzyme in the presence of an excess of substrate can cause an abnormally elevated production of galactitol or sorbitol in galactosemic subjects. Abnormal concentrations of polyols cause accumulations of these substances in the crystalline lens, in the peripheral nerves and in the kidneys of diabetic subjects. In fact, the intervention of aldose-reductase present in the tissues is hardly noticeable in a subject with normal glycaemia. Its role becomes much more important in diabetic subjects who have a much higher glycaemia.

In this way there is explained a modification of the capillary functions, of nerve conduction disorders and of the appearance of a diabetic cataract with loss of transparency of the crystalline lens.

Compounds of the invention may be helpful in reducing or totally avoiding these serious complications.

Moreover the compounds according to this invention decrease the prolactin secretion by the rat's hypophysis *in vitro* at a concentration of 10^{-6} M and above and *in vivo* at doses from 2 to 20 mg/kg. The basal secretion of the growth hormone is not modified in these conditions, but the hypersecretion provoked by a sympathetic stress is inhibited, which property can be of particular interest in the treatment of diabetics.

Consequently, compounds of the general formula I and their physiologically tolerable salts may be used for the treatment of diabetes, in particular, for combating the increase in the capillary permeability at the origin of retinopathy and trophic disorders, the prevention or the treatment of diabetic neuropathy in its peripheral or visceral manifestations and the prevention and the treatment of cataract and of diabetic nephropathy.

The present invention accordingly provides a pharmaceutical preparation which comprises a

compound of the general formula I or a physiologically tolerable salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier. The preparation may, for example, be in dosage unit form.

Preferably, the compounds of the invention are administered by the oral or parenteral route. The pharmaceutical forms which are most particularly suitable for such administrations include solutions and suspensions which are injectable, prepared in ampulles or in auto-injectable syringes; plain and coated tablets; sugar coated tablets; capsules; pills; drinkable syrups and emulsions; ointments; drops; collyria; and opthalmic gels and saccules (for the eyes).

The unit posology may vary according to the route of administration, the age of the patient and the severity of the therapeutic indication. It may range for example from 25 to 250 mg per unit dose. The daily posology may range for example from 50 to 500 mg in an adult.

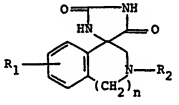
EXAMPLE OF A CAPSULE (EXAMPLE A)

6-chloro-2-benzyl-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione	50 mg
lactose	40 mg
talc	10 mg

for one capsule.

CLAIMS

1. A compound of the general formula:



I

in which

— R_1 represents a halogen or a hydrogen atom, or a hydroxy or methoxy group,

— R_2 represents a hydrogen atom, a lower alkyl radical, a phenyl-lower alkyl radical, a lower alkanoyl radical or a *p*-toluenesulphonyl group, and

— n represents 1 or 2,

in the racemic form or as an optical isomer.

2. A compound as claimed in claim 1, in which R_2 represents a hydrogen atom.

3. 6-Chloro-2-benzyl-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione.

4. 6-Chloro-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione or its (*l*) or (*d*) isomer.

5. 6-Fluoro-1,2,3,4-tetrahydro-isoquinoline-4-spiro-4'-imidazolidine-2',5'-dione.

6. 3-Acetyl-benzo-[d]-azepine-1-spiro-4'-imidazolidine-2',5'-dione.

7. A compound as claimed in claim 1, which is any one of those shown in the Table herein.

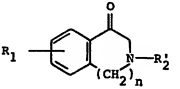
8. A salt of a compound claimed in any one of claims 1 to 7.

9. A salt of a compound claimed in any one of claims 1 to 7 with a mineral or organic base.

10. An acid addition salt of a compound claimed in any one of claims 1 to 5 and 7, with the exception of a compound in which R_2 represents an alkanoyl radical or *p*-toluenesulphonyl group.

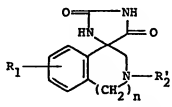
11. A salt as claimed in any one of claims 8 to 10, which is physiologically tolerable.

12. A process for the preparation of a compound as claimed in claim 1 or a salt thereof, which comprises condensing a compound of the general formula



II

in which R_2' has the meaning given for R_2 in claim 1, except that it may not represent a hydrogen atom, and R_1 and n have the meanings given in claim 1, or a salt thereof, with an alkali metal cyanide in the presence of ammonia or an ammonium salt to provide a compound of the general formula



I'

in which n, R_1 and R_2' have the meanings given above, or a salt thereof, and, if desired, carrying out one or more of the following steps in any appropriate order:
converting a compound of the general formula I' into a compound of the general formula I given in claim 1 in which R_2 represents a hydrogen atom; converting a compound of the general formula I into another compound of the general formula I; converting a compound of the general formula I' or I into a salt thereof.

13. A process as claimed in claim 12, in which a compound of the general formula I' produced in which R_2' represents a phenyl-lower alkyl radical is converted into a compound of the general formula I in which R_2 represents a hydrogen atom.

14. A process as claimed in claim 12 or claim 13, in which a compound of the general formula I in which R_2 represents a hydrogen atom is converted to a compound of the general formula I in which R_2 represents an alkanoyl radical or *p*-toluenesulphonyl group by acylation with a halide of a (lower alkyl)carboxylic acid or with a *p*-toluenesulphonyl halide.

15. A process as claimed in claim 12, carried out substantially as described in any one of the Examples herein.

16. A compound as claimed in claim 1, whenever prepared by a process as claimed in any one of claims 12 to 15.

17. A salt of a compound claimed in claim 1, whenever prepared by a process as claimed in any one of claims 12 to 15.

18. A physiologically tolerable salt of a compound claimed in claim 1, whenever prepared by a process as claimed in any one of claims 12 to 15.

19. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 7, 11, 16 and 18, in admixture or conjunction with a pharmaceutically suitable carrier.

20. A pharmaceutical preparation as claimed in claim 19, which is in dosage unit form.

21. A pharmaceutical preparation as claimed in claim 20, which contains from 25 to 250 mg of active ingredient per dosage unit.

22. A pharmaceutical preparation as claimed in claim 19, substantially as described in Example A herein.

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BH

ENGLISH ABSTRACT FOR SU1238732

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Title :
Alpha-2 antagonist compsn. contg. 3-benzazepine cpd. esp. for reducing intra=ocular pressure and blood pressure

Derwent Class :
B02

Patent Assignee :
(SMIK) SMITHKLINE BECKMAN CORP

Inventor :
DEMARINIS RM; HIEBLE JP; MATTHEWS WD

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19

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EP--80779
Regional States: AT BE CH DE FR GB IT LI LU NL SE

Abstract :
EP--80779 A
An alpha-2 antagonist compsn. comprises a carrier and a 3-benzazepine cpd. of formula (I) or its pharmaceutically acceptable acid addn. salt. (R is 1-3C alkyl or allyl. X is halo). Most pref. (I) is 6-chloro -2,3,4,5-tetrahydro-3-methyl-1H-benzazepine (Ia) used as its hydrochloride salt. Esp. (I) are used to reduce intraocular pressure (treatment of glaucoma); as cardiovascular agents (treatment of congestive heart failure, angina pectoris and thrombosis) and as antihypertensives. They have no direct effect on pupil size and no effect on heart rate or blood pressure in normotensive subjects.

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